GENETIC CORRELATION WITH THE DNA REPAIR ASSAY IN MICE EXPOSED TO HIGH-LET

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We hypothesize that DNA damage induced by high local energy deposition, occurring when cells are traversed by high-LET particles, can be experimentally modeled by exposing cells to high doses of low-LET. In this work, we validate such hypothesis by characterizing and correlating the time dependence of 53BP1 radiation induced foci (RIF) for various doses and LET across 72 primary skin fibroblast from mice. This genetically diverse population allows us to understand how genetic may modulate the dose and LET relationship. The cohort was made on average from 3 males and 3 females belonging to 15 different strains of mice with various genetic backgrounds, including the collaborative cross (CC) genetic model (10 strains) and 5 reference mice strains. Cells were exposed to two fluences of three HZE particles (Si 350MeV/n, Ar 350MeV/n and Fe 600 MeV/n) and to 0.1, 1 and 4 Gy from 160 kV X-ray. Individual radiation sensitivity was investigated by high throughput measurements of DNA repair kinetics for different doses of each radiation type. The 53BP1 RIF dose response to high-LET particles showed a linear dependency that matched the expected number of tracks per cell, clearly illustrating the fact that close-by DNA double strand breaks along tracks cluster within one single RIF. By comparing the slope of the high-LET dose curve to the expected number of tracks per cell we computed the number of remaining unrepaired tracks as a function of time post-irradiation. Results show that the percentage of unrepaired track over a 48 hours follow-up is higher as the LET increases across all strains. We also observe a strong correlation between the high dose repair kinetics following exposure to 160 kV X-ray and the repair kinetics of high-LET tracks, with higher correlation with higher LET. At the in-vivo level for the 10 CC strains, we observe that drops in the number of T-cells and B-cells found in the blood of mice 24 hours after exposure to 0.1 Gy of 320 kV X-ray correlate well with slower DNA repair kinetics in skin cells exposed to X-ray. Overall, our results suggest that repair kinetics found in skin is a surrogate marker for in-vivo radiation sensitivity in other tissue, such as blood cells, and that such response is modulated by genetic variability.